REMARKS

Status of Claims

Claims 1, 10 and 11 are all the claims pending in the application. Claims 1, 10 and 11 are rejected.

Information Disclosure Statements

Applicants thank the Examiner for previously acknowledging the Information Disclosure Statements filed September 9, 2003, December 22, 2004 and October 24, 2006, by returning signed and initialed copies of the PTO Forms SB/08 that were submitted therewith.

Claim to Priority

Applicants thank the Examiner for acknowledgement of Applicants' claim of priority to Japanese Application No. P. Hei 10-131815 filed May 14, 1998, as well as receipt of a copy of the priority document in U.S. Application No. 09/700,397, of which the present application is a divisional thereof.

Withdrawal of Objections/Rejections

Applicants thank the Examiner for withdrawal of the rejections of (1) Claims 1 and 10 under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description, (2) new matter rejections for claims 1, 2, and 10 under 35 U.S.C. 112, first paragraph, and (3) claims 1, 2, and 10 under 35 U.S.C. 112, second paragraph.

Response to Claim Rejections Under 35 U.S.C. § 101

On page 3 of the Office Action, the Office Action rejects Claims 1, 10, and 11 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility, or a well established utility. The Office Action asserts

that Applicants' comments submitted in the response filed September 11, 2007 have been fully considered, but are unpersuasive for the following reasons.

1. First, the Office Action admits that the originally-filed specification discloses "significant homology" between clone OC001 and rat neurotrimin and between clone OC001 and OBCAM. The Office Action also acknowledges that the specification discloses that, based upon such homology, the proteins are expected to share some activity.

However, the Office Action appears to suggest that such a showing is insufficient to satisfy the requirement for utility, because (a) it is allegedly known in the art that the positions in which amino acid substitutions can be made with a reasonable expectation of success are limited and (b) the art reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities (see U.S. Patent No. 5,194,596; Benjamin *et al.*, 1998, *Development* 125:1591-1598; Vukicevic *et al.*, 1996, *PNAS USA* 93:9021-9026; Massague *et al.*, 1987, *Cell*, 49:437-8; Pilbeam *et al.*, 1993, *Bone* 14:717-720 and; U.S. Patent No. 5,350,836).

Initially, Applicants note that the Examiner's position that OC001 does not have utility, due to the unpredictability of gene mutagenesis, lacks merit. Even if the Office Action's allegations of unpredictability were to be substantiated, the Examiner's argument is flawed because it assumes that the functionality of polypeptides that have evolved through natural selection is comparable to that of mutant proteins that result from gene mutagenesis *in vitro*. The Office Action's reasoning is actually rebutted by the document cited to support the Office's position in the Office Action of February 12, 2007, namely Kopchick *et al.* Although Kopchick *et al.* disclose a mutant bovine growth hormone (through mutation of residue 119) that exhibits growth-inhibition activity, nothing in Kopchick *et al.* suggests that such a mutation may be found

in naturally occurring homologues. To the contrary, in column 7, lines 5-8, Kopchick *et al.* disclose that the glycine at residue 119 is conserved in "all of the growth hormones noted by Watahiki" which upon review of Watahiki *et al.* is found to include growth hormones from highly diverse species, such as salmon, tuna, chicken, rat, porcine, ovine, bovine and human. Thus, one of ordinary skill in the art reading Kopchick *et al.* would more likely than not understand quite the opposite to that inferred by the Office Action, that is, that those residues that when mutated cause a loss of function, are conserved in homologues from even highly divergent species. The Kopchick *et al.* reference actually supports the position that protein homologues share similar activities, thus weakening the Office Action's position.

With regard to point (b), the Office Action cites a multitude of references to support the argument that even proteins within the same family may exhibit different, or perhaps opposing effects. However, these references cannot reasonably be applied to support a rejection for lack of utility of the instant polypeptide, because the references do not pertain to regulators of neurite outgrowth. Rather, the cited references concern growth factors that mediate their effects in the periphery, such as transforming growth factors (TGF-beta), parathyroid hormone-related peptide and vascular-endothelial growth factors. Thus, first, the Office Action has failed to demonstrate that homologous proteins involved in neurite outgrowth may have unpredictable activities. To the contrary, the references submitted by Applicants support the conclusion that neurotrimin and its homologues have similar activities (i.e. homophilic interaction-induced neurite outgrowth; inhibition by heterophilic interaction).

Second, although the Office Action alleges that the cited documents disclose "examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities," the Office Action does not disclose the degree of relatedness between such

proteins. In the reply filed September 11, 2007, Applicants point out that OC001 has 70% homology to rat neurotrimin and 91% homology to opioid-binding cell adhesion molecule. One of ordinary skill in the art would have an expectation that OC001, neurotrimin and opioid-binding cell adhesion molecule would have similar properties in view of the high level of sequence homology. Unlike the TGF-beta family mentioned by the Office Action, which encompasses a wide variety of diverse proteins, Applicants did not speculate upon a function for OC001 from sequence homology with distantly related proteins, but rather, have identified OC001 as an IgLON family protein, a small and highly related genus of neuronal proteins.

Thus, the Office Action has failed to reasonably consider the high degree of relatedness between members of the IgLON subfamily, the small size of the IgLON genus, and the shared activities of characterized IgLON proteins. Considering that OC001 is human neurotrimin, and thus is a *bona fide* member of the IgLON subfamily, one of ordinary skill in the art would have a presumption that OC001 modulates neurite outgrowth. For at least these reasons, the references provided to the Office Action in the reply filed September 11, 2007 demonstrate utility of IgLON proteins as modulators of neurite outgrowth.

Accordingly, for at least these reasons, and the state of the art as of the effective filing date, one of ordinary skill in the art would understand that IgLON proteins are well-established as modulators of neurite outgrowth, and that the identification of OC001 as human neurotrimin firmly establishes that OC001 has a credible specific and substantial utility as a regulator of neurite outgrowth.

Reconsideration and withdrawal of the rejection under § 101 is respectfully requested.

2. Next, the Office Action asserts that the instant specification discloses an extensive list of biological activities that the OC001 polypeptide may exhibit. Further, the Office Action

alleges that the specification does not clearly disclose that OC001 causes neurite outgrowth. The Office Action contends that Applicant has now purportedly identified that OC001 causes neurite outgrowth, but that the instant specification makes clear that a specific and substantial utility for OC001 was neither disclosed in the specification, nor well known in the art as of the effective filing date.

The Office Action cites *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005), asserting that a substantial utility requires a "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research" and that a specific utility is "a use which is not so vague as to be meaningless." The Office Action relies on *In re Fisher* to maintain the rejection under 35 U.S.C. § 101, alleging that the OC001 polypeptide has been isolated due to its similarity to known proteins. The Office Action asserts that "there is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility [but until] further characterization … Applicants' claimed invention is incomplete."

Initially, Applicants note that the state of the art as of the effective filing date is sufficient to establish that IgLON subfamily proteins modulate neurite outgrowth. The high homology between OC001 and rat neurotrimin and between OC001 and opioid-binding cell adhesion molecule, and the identification of OC001 as human neurotrimin, places OC001 firmly within the IgLON subfamily. Thus, despite the recitation of other functions within the specification, the state of the art clearly teaches that IgLON subfamily members regulate neurite outgrowth, and the data provided by Applicants clearly confirms OC001 as an IgLON protein.

Second, the Office Action's reliance on *In re Fisher* is inapt, considering the differences between the claimed subject matter. Specifically, *In re Fisher* concerned the utility of expressed-

sequence tags (ESTs) of known nucleotide sequence, in which appellants claimed the ESTs had utility as a nucleotide sequence alone, such as a research tool for monitoring gene expression by measuring the level of mRNA through microarray technology and in identifying the presence or absence of polymorphisms. The proteins encoded by the ESTs were not ascribed a predicted function based on sequence similarity to known cDNAs, and the utility of the ESTs was not argued with regard to utility of the proteins encoded by the ESTs. Accordingly, the finding of a lack of utility in *In re Fisher* for ESTs which encode proteins without any predicted function is factually distinct from the instant case, where the state of the art at the time of filing strongly suggests that OC001 is an IgLON protein that moduates neurite outgrowth.

Reconsideration and withdrawal of the rejection under § 101 is respectfully requested.

3. Further, the Office Action contends that the state of the art is such that IgLON family members, which include neurotrimin and OBCAM, are expressed on distinct populations of neurons, and have opposing activities on different types of neurons. The Office Action notes that the instant application does not disclose those cells that express the claimed OC001 polypeptide. To further support this position, the Office Action refers to Gil *et al.* (Gil I), who allegedly conclude that the distinct expression of IgLON members promotes the development of system-specific projections by a combination of growth-promoting and growth-inhibiting activities and that the precise signaling pathways involved and the functional consequences of interactions between different family members are important questions for future investigation. From this, the Office Action maintains the position that the function of OC001 would be unpredictable.

As previously discussed above, the references cited by the Office Action do not demonstrate that the function of IgLON proteins is unpredictable. Rather, Gil I demonstrates in

a series of experiments that a clear correlation exists between the induction of neurite outgrowth and the presence of neurotrimin on the target cell membrane. Further, Gil I indicates that the homophilic interaction between soluble neurotrimin and membrane-bound neurotrimin on the target cell membrane leads to induction of neurite outgrowth. Conversely, Gil I also demonstrates that in cells lacking membrane-bound neurotrimin, such as SCG cells, a heterophilic interaction mediates inhibition of neurite outgrowth. Gil I discloses that these results are in accordance with the results of another IgLON member, namely gp55, which when added to chick E9 DRG neurons, triggers inhibition of neurite outgrowth. Gil I specifically points out that these neuronal cells do not express membrane-bound gp55, thus no homophilic interaction can occur. This correlation is further supported by Gil I on page 9323 where it is disclosed that LAMP, another IgLON member, inhibits the outgrowth of neurons expressing low levels of membrane-bound LAMP, but high levels of neurotrimin. Thus, the data proffered by Gil I supports a role for induction of neurite outgrowth via homophilic interaction, and a role in inhibition of neurite outgrowth in the absence of a homophilic interaction. Further, in the McNamee *et al.* reference cited by the Office Action, McNamee *et al.* admits that "LAMP can act as a bifunctional agent on neuronal outgrowth, enhancing the extension of neurites from thalamic neurons expressing LAMP, whilst inhibiting growth from thalamic neurons which do not." Accordingly, the state of the art, and particularly those references relied upon by the Office Action, support a predictable function for IgLON family members in regulation of neurite outgrowth.

Further, one of ordinary skill in the art would be able to predict those cell types in which neurite outgrowth would be expected, by detecting levels of specific IgLON proteins on target cell membranes. The references cited by the Office Action, for example Gil I, disclose methods

for identifying cells in which IgLON members are expressed in large amounts on the cell surface, such as by immunofluorescence (see Figure 4). Thus, one of ordinary skill in the art would be able to predict for a given cell type whether neurite outgrowth or inhibition would occur.

Reconsideration and withdrawal of the rejection under § 101 is respectfully requested.

4. In response to Applicants' comments submitted September 11, 2007 that the McNamee *et al.* reference is not representative of the general state of the art, the Office Action has found these arguments unpersuasive. Specifically, the Office Action maintains that McNamee *et al.* confirm that as of 2002, there was inconclusive evidence for a role of IgLON members in neurite outgrowth. The Office Action alleges that McNamee *et al.* admit that their studies failed to find conclusive evidence for a role of IgLON members in neurite outgrowth or axon guidance. In view of McNamee *et al.*, which the Office Action alleges to be representative of the state of the art as of 2002, the Office Action alleges that one of ordinary skill in the art would not know the functional activity of the purported IgLON family member, OC001.

In response, Applicants note that McNamee *et al.* is not representative of the art as a whole, but rather, that the art suggests that IgLON proteins are involved in modulating neurite outgrowth. In this regard, Applicants submit Gil *et al.* (Gil II)[1], Neurobiology 51(3): 190-204 (2002), which further supports the concept that homophilic interaction among IgLON family members promotes neurite outgrowth while heterophilic interactions inhibit neurite outgrowth.

[1] In accordance with M.P.E.P. 609(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

The teachings of Gil II were presented in 2002, when McNamee *et al.* was also published and supports this mainstream concept.

Thus, with regard to the function of the IgLON family, the teachings of McNamee *et al.* were not the mainstream, and not representative of the art as a whole.

Reconsideration and withdrawal of the rejection under § 101 is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112

On page 9 of the Office Action, the Office Action rejects Claims 1, 10, and 11 under 35 U.S.C. 112, first paragraph. The Office Action contends that because the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility, one of ordinary skill in the art would not know how to use the claimed invention. The Office asserts that the basis for this rejection is set forth at page 9 of the previous Office Action (12 February 2007) and at page 8 of the Office Action of 07 June 2006.

The Office Action asserts that Applicants have not provided sufficient evidence to demonstrate that the OC001 polypeptide has a specific and substantial utility, or a well established utility, and thus one of ordinary skill in the art would not know how to use the claimed invention. Further, the Office Action asserts that the instant specification is required to teach one of ordinary skill in the art how to make and use the CO001 polypeptide in order to satisfy the requirements under 35 U.S.C. § 112.

In response, and as discussed above, one of ordinary skill in the art would have understood that the claimed isolated polypeptide has a role for induction of neurite outgrowth via homophilic interaction, and a role in inhibition of neurite outgrowth in the absence of a homophilic interaction, and that such a role supports both a specific and substantial utility under 35 U.S.C. §101.

Further, one having ordinary skill in the art would understand, following the guidance in Applicants' specification, e.g., the Examples in the originally filed specification which describes how to isolate the nucleic acid encoding the claimed protein, to make the claimed polypeptide from this nucleic acid molecule. Further, such common techniques were very well known in the art at the time of filing, and the protein expression from such an isolated nucleic acid is routine and predictable.

Thus, the subject matter recited in the claims is enabled so that one of ordinary skill in the art would be capable of practicing Applicants' claimed invention without undue experimentation.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

Tu A. Phan, Ph.D.
Registration No. 59,392

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON DC SUGHRUE/265550

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